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SYNTHESIS OF CYCLIC ETHERS BY RHODIUM CARBENOID CYCLISATION

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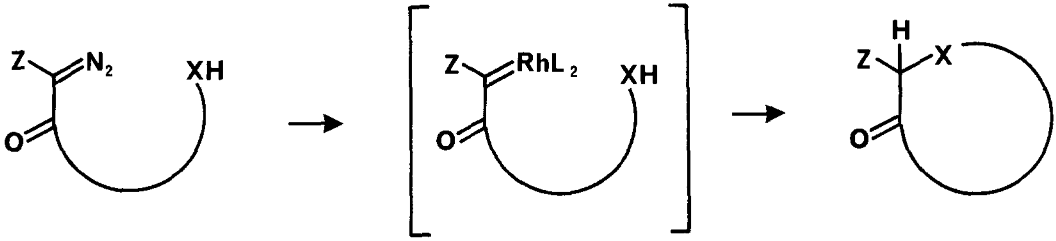
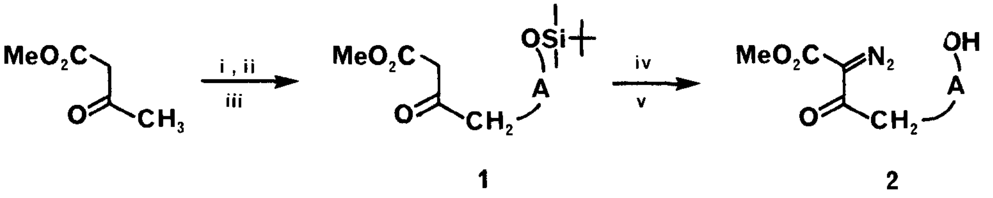
Summary: Treatment of the diazocarbonyl compounds (**2**), readily prepared in 3 steps from methyl acetoacetate, with a catalytic amount of rhodium (II) acetate, leads to the formation of the cyclic ethers (**3**).

The rhodium (II) catalysed decomposition of diazocarbonyl compounds is believed to involve a metallo-carbenoid intermediate which retains the highly electrophilic properties associated with free carbenes.[1] Therefore, in an appropriate acyclic substrate, such an intermediate would be intercepted intramolecularly by a nucleophile to effect overall cyclisation. Although examples of such cyclisations, shown in general in Scheme 1, are known,[2,3] the reaction has not been widely exploited in synthesis. Hence we have been interested in exploring the potential of rhodium carbenoid cyclisations as a general route to oxygen-, sulphur-, and nitrogen-containing rings (Scheme 1, X = O, S, NR), and we now report our preliminary results on the first use of this method in the synthesis of 7- and 8-membered ring ethers.[4,5]



Scheme 1

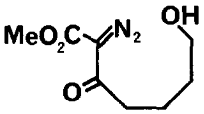
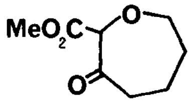
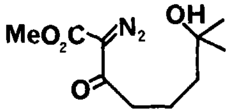
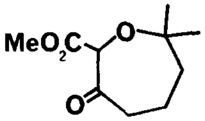
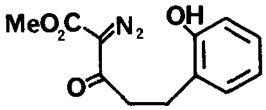
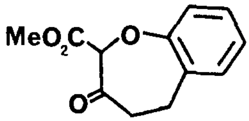
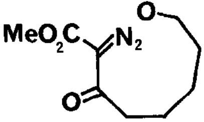
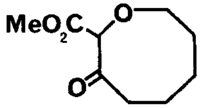
The starting diazocarbonyl compounds (**2**) were prepared in 3 steps from readily available materials (Scheme 2). Thus methyl acetoacetate was converted into its dianion, and alkylated with a t-butyldimethylsilyl (TBDMS) protected α,ω-haloalcohol (Table) to give the β-ketoesters (**1**) (43-74%). Diazo-transfer to (**1**) using tosyl azide in acetonitrile in the presence of triethylamine proceeded easily (76-98%), and removal of the TBDMS-group in the presence of the diazo function to give the required diazo compounds (**2**) was achieved by the use of aqueous acetic acid or aqueous hydrofluoric acid (62-79%).



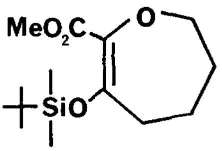
Scheme 2. Reagents: i, NaH, THF; ii, BuLi; iii, Hal-A-OTBDMS (Table); iv, TsN_3, Et_3N, MeCN; v, $AcOH-H_2O-THF$ or $HF-H_2O-MeCN$.

The cyclisation of diazo compound (**2a**) occurred readily in refluxing benzene in the presence of a catalytic amount of rhodium (II) acetate to give the 3-oxo-oxepane (**3a**) in good yield (Table). The reaction is not subject to steric hindrance at the oxygen centre, the tertiary alcohol (**2b**) cyclising just as easily, in 72% yield. Similarly, cyclisation of the phenol (**2c**) gave the 3-oxotetrahydrobenzoxepin (**3c**) (71%), and the diazo compound (**2d**) gave the 3-oxo-oxocane (**3d**) in modest yield (Table).

Table. Rhodium (II) Acetate Catalysed Cyclisations

	Hal-A-OTBDMS	Diazo Compound (**2**)	Cyclic Ether (**3**)	Yield (%)
a;	$I(CH_2)_3OTBDMS$			78
b;	$I(CH_2)_2CMe_2OTBDMS$			72
c;	$BrCH_2-C_6H_4-OTBDMS$			71
d;	$I(CH_2)_4OTBDMS$			24

The structures of the cyclised products (**3**) were supported by their spectral properties, although the n.m.r. spectra were complicated by the presence of both keto and enol tautomers of the cyclic β-ketoesters. However, the n.m.r. spectra of the corresponding TBDMS-enol derivatives, for example (**4**) prepared by treatment of (**3a**) with TBDMS-triflate, were much simpler and easier to assign. The 3-oxo-oxepane (**3a**) also reacted with benzylamine to give the crystalline enamine (**5**), m.p. 115-117°C, the structure of which was confirmed by X-ray crystallography (Figure).[6,7]



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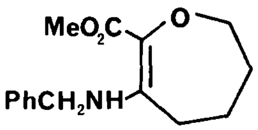

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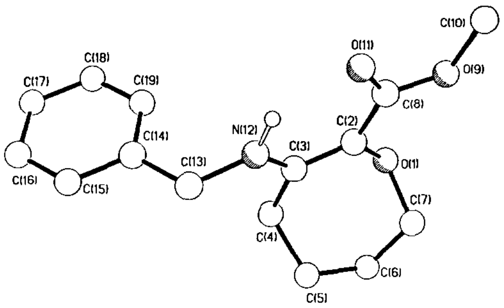

Figure. X-Ray Crystal Structure of Methyl 3-Benzylamino-4,5,6,7-tetrahydro-oxepin-2-carboxylate (**5**) (showing crystallographic numbering).

Thus the rhodium carbenoid cyclisations to 7-membered ring ethers occur easily in good yield. Although OH bonds are thermodynamically stronger than CH bonds, competing CH insertion reactions are not a problem, providing further evidence that the reaction proceeds by nucleophilic attack on a rhodium carbenoid intermediate.[4] The formation of the 8-membered ring ether, albeit in modest yield, is particularly noteworthy since 8-membered rings are among the most difficult to form by any ring closure method.[8,9]

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References

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5. There are isolated examples of 5- and 6-membered ring ether formation in other carbene-reactions: H.G. Davies, S.M. Roberts, B.J. Wakefield, and J.A. Winders, *J. Chem. Soc., Chem. Commun.*, 1985, 1166; T. Harada, E. Akiba, K. Tsujimoto, and A. Oku, *Tetrahedron Lett.*, 1985, **26**, 4483.
6. Crystal data: $C_{15}H_{19}NO_3$, $\underline{M}$ = 261.3, monoclinic, space group $\underline{P2_1/a}$, $\underline{a}$ = 9.168(1), $\underline{b}$ = 13.747(1), $\underline{c}$ = 11.628(1) Å, β = 111.91(1)°, $\underline{U}$ = 1360 Å^3, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.29 gcm^{-3}. 1331 Independent observed reflections [$|\underline{F}_o| > 3\sigma(|\underline{F}_o|$, $\theta < 50°$] were measured on a Nicolet R3m diffractometer with Cu-$\underline{K}_\alpha$ radiation (graphite monochromator) and using ω-scans. The structure was solved by direct methods, and the non-hydrogen atoms refined anistropically. All hydrogen atom positions were idealised with the exception of H(12) which was located in a $\Delta\underline{F}$ map and refined isotropically. Refinement converged to $\underline{R}$ = 0.033, $\underline{R}_w$ = 0.041 [$w^{-1} = \sigma^2(\underline{F}) + 0.00025\,\underline{F}^2$]. There is an intramolecular hydrogen bond between N(12) and O(11) [N(12)--O(11) 2.69, H(12)--O(11) 1.95 Å, $\widehat{\text{N(12)--H(12)--O(11)}}$ 131°]. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[7] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.
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9. For a recent exception see G.S. Cockerill, P. Kocienski, and R. Threadgold, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2093.

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